Heart Failure Pharmacology

Introduction

This lesson is about the management of systolic heart failure, most accurately labeled Heart Failure with reduced Ejection Fraction (HFrEF).

Diastolic heart failure, Heart Failure with preserved Ejection Fraction (HFpEF), is almost always synonymous with hypertensive heart disease, a "concentric concentric hypertrophy" of the left ventricle. Diastolic heart failure is managed by controlling the blood pressure. Treating hypertension treats diastolic failure. Those cardiomyopathies that result in a diastolic dysfunction that is not hypertensive heart disease have their own specific treatments, and should be learned in context of the disease (for example, HOCM is treated with β-blockers and avoidance of dehydration, discussed in Structure and Function #8: *Cardiomyopathy*).

The classes in this lesson are described in detail elsewhere in the course. We will NOT review all the side effects and contraindications, nor review the names of the classes. The goal of this lesson is to use the pathophysiology of heart failure and the mechanism of action of the drugs and align our trusty MAP equation to treat heart failure. Like we did for hypertension (Hemodynamics #6: *Hypertension Pharmacology*), you will be getting a preview of clinical management in this lesson, taught from the perspective of mechanisms.

Pathophysiology of Heart Failure

Chronic activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system is associated with ventricular remodeling, loss of myocytes, myocyte hypertrophy, and fibrosis. The initial stimulus is compensatory. Sustained stimulation induces progression of heart failure.

β_1 stimulation initially results in an increased calcium conductance, an increase in contractility (and heart rate). Chronically, β_1-stimulation is the trophic signal that induces cardiac myocyte remodeling and ventricular remodeling.

α_1 stimulation increases the resistance of arterioles, and thereby increases systemic vascular resistance, and is one of the mechanisms that induces afterload-overload heart failure. As in the treatment of hypertension, α_1 receptors aren't the primary target.

Angiotensin 2 is the product of the RAAS. It both tenses the angios, increasing SVR, and is one of the mechanisms that induces afterload-overload heart failure. Worse, angiotensin-receptor stimulation sensitizes the cardiac myocytes to β_1-stimulation, exacerbating the trophic signal that causes the addition of sarcomeres. Angiotensin 2 is also the driving force behind aldosterone expression, which in turn leads to preload-overload heart failure.

Aldosterone (sodium, volume, preload, EDV) reabsorbs sodium from the collecting duct of the nephron. Water follows salt. Aldosterone contributes to preload-overload heart failure.

Not surprisingly, then, the management of chronic heart failure involves blocking β_1 (β-blockers), blocking the effects of α_1 (arterial dilators such as hydralazine), blocking the effects of angiotensin 2 (angiotensin-converting enzyme inhibitors, ACE-i or angiotensin-receptor blockers, ARBs), blocking aldosterone (spironolactone), and getting rid of excess volume (loop diuretics).

Nonpharmacological Treatment

Systolic heart failure starts as a contractility issue and ends as a volume issue. With a failing heart, with weakened contractility, increases in preload worsen the Frank-Starling mechanism. Rather than improving the force of contraction, overstretch of myocytes by excess volume only further weakens the force of contraction. Increased volume leads to fluid overload—fluid on the lungs and in the periphery. Water follows salt. Therefore, the general strategy for the treatment of heart failure becomes volume and salt restriction. The goal is **< 2 L fluid** and **< 2 g NaCl** per day.

The kidneys' perception of volume status is dictated by GFR—reduced GFR kicks off the RAAS. Avoidance of substances that impair GFR becomes critical. Patients with HFrEF **should avoid NSAIDs**.

NYHA Classification

The extent of structural changes does not correlate with symptom activity or management. There was a categorization of structural changes that ranked the heart from A to D. If you see letters in relation to heart failure, ignore them. Prognosis and management decisions are based on the patient's functional classification as described by the New York Heart Association.

NYHA CLASS	SYMPTOMS (FROM THE NYHA)	PRACTICALLY (FROM OME)
I	No limitations in normal physical activity	Dyspnea with running a mile
II	Mild symptoms only in normal activity	Dyspnea climbing a flight of stairs
III	Marked symptoms during daily activities	Dyspnea walking on flat surface
IV	Severe limitations, symptoms at rest	Dyspnea at rest

Table 7.1: NYHA Classification

Treatment of heart failure is based on the NYHA class.

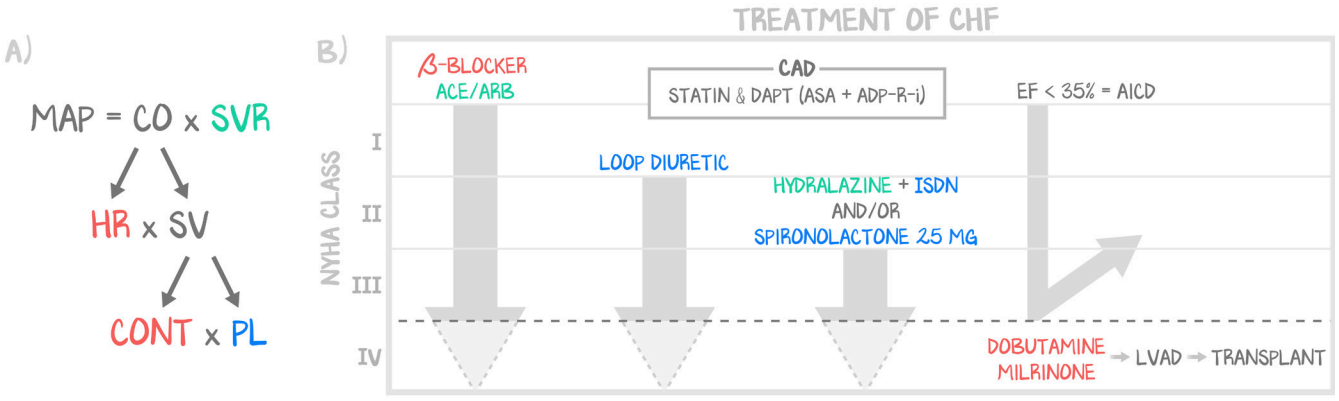

Figure 7.1: Treatment of CHF
All classes are recommended ACE inhibitors and β-blockers. Once signs of fluid overload develop, class II and worse, loop diuretics are added. As symptoms worsen, class III and worse, or as additional blood pressure control can be tolerated, spironolactone and/or BiDil® are added. Class IV patients depend on inotropic agents for survival. If the EF is < 35% and not class IV, refer for AICD. If ischemic cardiomyopathy, add antiplatelets (aspirin and an ADP-receptor antagonist) and statin therapy to the β-blocker and ACE inhibitor. Notice the color-coordination with the elements of the MAP equation.

Medications and Justifications

β-blockers. While it may seem counterintuitive to give an agent that obviously reduces ventricular contractility to an already-impaired ventricle, β-blockers are indicated in **every class of systolic heart failure**. β-blockers **reduce mortality in all systolic heart failure**. We've set you up to see that the benefits outweigh the risks. Sustained adrenergic stimulation is what causes myocyte hypertrophy, and the hypertrophy causes the reduced ejection fraction. Blocking β_1 prevents the direct cause of ventricular remodeling. Other benefits include blunting renin release, thereby also reducing the RAAS to a small extent. β-blockers work on pacemaker myocytes as well, reducing heart rate, further reducing ventricular work, enabling those already hypertrophied myocytes to work less. β-blockers are contraindicated in acute CHF exacerbations, as they DO reduce contractility upon initiation. **Never start or increase a β-blocker until a patient is euvolemic.** Once they are euvolemic (not in an exacerbation), β-blockers are absolutely indicated. The names are on the last page. The only β-blockers you should use in heart failure are **metoprolol succinate**, **carvedilol**, and bisoprolol. Metoprolol (no blood pressure effects, β_1 only, rate control) and carvedilol (α_1- and β_1-blocker, blood pressure reduction) are the only β-blockers we recommend learning for cardiovascular disease, period. Metoprolol is preferred when heart rate reduction is desired without the need for blood pressure reduction (CHF with AFib). Carvedilol is preferred when both heart rate reduction and blood pressure reduction are desired (systolic heart failure and hypertension).

ACE/ARBs. The obvious benefit of ACE/ARBs is to inhibit the RAAS. ACE/ARBs prevent Ang 2 from "tensing the angios," therefore ACE/ARBs lead to a reduced afterload. Afterload is the second stressor that leads to myocyte hypertrophy, and an already-compromised ventricle will have an easier time restoring forward flow with less afterload. ACE/ARBs also blunt aldosterone secretion, preventing excess preload. But ACE/ARBs have a **mortality benefit beyond afterload reduction and preload reduction**. We know this because achieving the same hemodynamic effects with BiDil® (hydralazine/isosorbide dinitrate), which reduces both preload and afterload, and spironolactone (inhibition of aldosterone) does not have as an improved mortality as with ACE/ARBs. The benefit is thought to be a reduction in epinephrine, seen in patients with heart failure. Less epinephrine, less β_1 stimulation. All ACE/ARBs are equivalent to one another.

The addition of a new medication, **sacubitril**, to an ARB has recently gained in popularity. Sacubitril is a **neprilysin inhibitor** that sustains ANP signaling by inhibiting ANP degradation. New combination medications that have poor initial study designs are suspect to us here at OME. A "landmark study" compared half-max-dose lisinopril to max-dose losartan, and max-dose losartan did better. You didn't read that wrong. What they actually did was compare half-max-dose lisinopril to max-dose losartan-with-sacubitril, and accounted the benefits to the sacubitril. Since then, further studies have shown that it was likely a poor study design but a good idea. And since the mechanism makes a lot of sense—ANP antagonizes aldosterone but aldosterone always wins, but by increasing the ANP by inhibiting the enzyme that degrades it, the ANP effect is greater, and so does a better job of antagonizing aldosterone.

The two medications that are essential for every patient with systolic heart failure seem to belong to two separate classes, but end up functioning synergistically with one another. β-blockers' primary effect is to block β_1 stimulation, but they also blunt the RAAS. ACE/ARBs directly inhibit the RAAS and its effects, but also blunt sympathetic stimulation. Other medications are ancillary. They are added if symptoms worsen or if blood pressure reduction is desired after the β-blockers and ACE/ARBs are maximized.

Maximize the ACE/ARB and β-blocker before adding additional agents.

Diuretics. If volume is the patient's issue, they should restrict volume and salt. If that doesn't work, give them diuretics. Loop diuretics such as furosemide are useful for relieving the symptoms of congestion—they **remove excess volume** and **make the patient feel better**. Their chronic use does not influence mortality. Diuresis does reduce preload, which improves cardiac function in an overloaded state. Diuresis

also reduces circulating plasma volume, which helps reduce blood pressure. They are used in intravenously when treating acute heart failure exacerbations in order to achieve euvolemia. Intravenous dosing is require because bowel edema may limit absorption when taken oraly. They are used orally in chronic patients who suffer from volume overload (NYHA class II and greater). You will use diuretics. You should use diuretics. β-blockers and ACE/ARBs affect mortality. Diuretics make the patient feel better.

Veno-vaso-dilators. The specific combination of isosorbide-dinitrate (venodilator) and hydralazine (arterial vasodilator) achieves the reduction in preload and afterload known to be beneficial from ACE/ARBs. Before ACE/ARBs were studied, this combination, known as BiDil®, was the preferred agent to treat systolic heart failure. This agent is used when the β-blocker and ACE/ARB have been maximized, the patient is on diuretics, and the current blood pressure will tolerate further reductions OR when the patient is intolerant to ACE/ARBs where hydralazine-ISDN is used in their stead. The combination does reduce preload (venodilation) and afterload (vasodilation).

Aldosterone antagonists. Spironolactone is the "other class III medication." It is an alternative option to BiDil® for class III heart failure. Being an aldosterone antagonist, its main effect is on reduction in preload. Because ACE/ARBs cause hyperkalemia, and AA's cause hyperkalemia, caution is warranted. You will not be asked to choose between spironolactone and BiDil® at this stage of training.

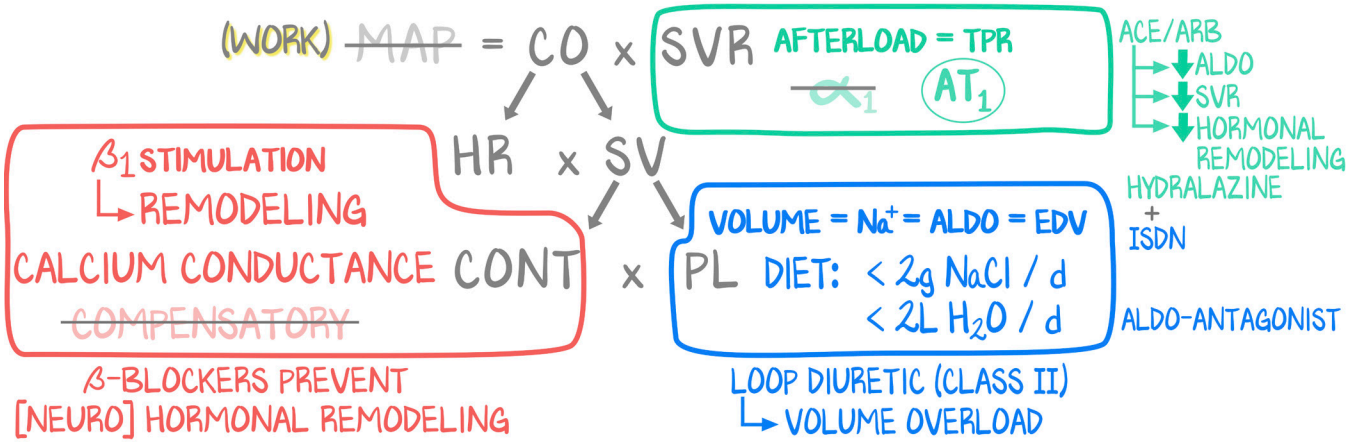

Figure 7.2: MAP Equation on CHF Drugs
The MAP equation can be used to categorize the treatment of chronic (that is, not in exacerbation) congestive heart failure. β-blockers offer a drawback and a benefit. When used acutely, the decrease in calcicum conductance conductance worsens contractility, reducing the ejection fraction. Used at the wrong time—when the patient is volume overloaded—and the acute use of β-blockers can precipitate cardiogenic shock. Chronically, when initiated at the right time—when the patient is dry—the longterm inhibition of β1 prevents the deleterious effects of neurohormonal remodeling, improving mortality. ACE inhibitors and ARBs not only improve the afterload, lifting the load from the heart, but they also prevent the remodeling of the heart (synergistically with β-blockers). Hydralazine is an afterload reducer as well, which does show improved outcomes. But because it fails to act on neurohormonal remodeling at all, it is reserved for use with ISDN. Finally, because HFrEF is all about fluid, symptomatic treatment for volume overload comes by way of loop diuretics. Don't forget salt and fluid restriction.

Inotropes. Inotropes are indicated only in class IV heart failure, as a bridge to transplant, or in cardiogenic shock. Dobutamine and milrinone must be constantly infused, and are stored in a pump. The activation of β_1 increases contractility, increasing the work of the heart. This will cause further degeneration of the cardiac function, effectively giving the pathologic stimulation by the autonomic nervous system an extra pathologic boost. They are used in acute CHF exacerbations with cardiogenic shock, and chronically in class IV patients who, without transplant, will die. With a transplant or bridge device, the deterioration of their current heart is irrelevant. They need the sustained contractile support to survive to the transplant. Most do not survive. Stimulation of β_2 receptors in skeletal muscle causes a vasodilation, which also serves to decrease afterload. We covered these in the Hemodynamics island.

Ischemic Cardiomyopathy

Ischemic cardiomyopathy is treated like coronary artery disease—β-blockerACEinhibitorStatinAspirinDAPT. Good news, the β-blocker and ACE inhibitor mandated by coronary artery disease are the same β-blocker and ACE inhibitor mandated by heart failure management. This means that ischemic cardiomyopathy, in addition to routine heart failure medications, requires only aspirin, DAPT, and a statin. DAPT stands for dual antiplatelet therapy, where both an aspirin and some other antiplatelet agent are used to prevent rupture and thrombosis of a plaque. This is discussed in detail in CAD #4: *Chronic Ischemic Heart Disease Pharmacology*. Here, DAPT acts as the stand-in for the second antiplatelet agent, one you haven't yet studied with us.